PAG: A POTENTIAL TUMOUR SUPPRESSOR AND HOW IT ALL STARTED. FROM IMMUNE SIGNALLING TO NEOPLASTIC TRANSFORMATION

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Souhrn

PAG: Možný nádorový supresor a jak to bylo na počátku. Od imunní signalizace k nádorové transformaci

Phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG), rovněž známý jako Csk-binding protein byl plně charakterizován v roce 2000. V původních studiích byl PAG rozpoznán jako ubikvitní adaptorový protein, který váže cytoplazmatickou C-koncovou Src-kinázu (Csk) do těsné blízkosti Src-kináz zakotvených v cytoplazmatické membráně, což umožnuje, aby Csk uplatnila svůj inhibiční vliv na tyto kinázy. Úloha PAGu byla původně spatřována v negativní regulaci imunitních reakcí. Od roku 2000 byly objeveny další na Csk závislé i nezávislé interakce, z nichž některé měly v experimentu anti-onkogenní účinky. Podle současných názorů staví tato pozorování PAG do role kandidáta na nádorový supresor.

Klíčová slova: PAG – Cbp – imunní signalizace – onkogeneze

Summary

Phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG) also known as Csk-binding protein was first fully characterized in 2000. It was initially recognized as a ubiquitously expressed adaptor protein recruiting cytoplasmic C-terminal Src-kinase to the close proximity of plasma membrane-anchored Src-kinases thereby allowing Csk to impose its inhibitory potential on these kinases. A role of PAG was initially seen in negative regulation of immune reactions. Since the year 2000 other Csk-dependent and independent interactions have been discovered and some of them showed anti-oncogenic effects in experiment. According to current opinions, these findings place PAG in a position of tumour suppressor candidate.

Key words: PAG – Cbp – immune signalling – oncogenesis

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PAG – A MISSING ADAPTOR PROTEIN

It was not the singularity at the *'PAG Big Bang'* but teams of researchers determined to crack the puzzle of interactions between membrane-bound immunoreceptors and the downstream cytoplasmic signalling molecules known to translocate to lipid rafts (specialised microdomains of the plasma membrane important for cell signalling) in response to receptor stimulation. In other words the scientific teams were looking for a missing link or a particular adaptor protein(s) (16). Indeed, the verge of the second millennium turned out to be notably successful as by 2002 the quartet of so far identified lipid raft-associated transmembrane adaptor proteins (RATRAPs) of haematolymphoid cells was discovered with a substantial contribution by Czech scientists (5-7). The currently recognized RATRAPs of haematolymphoid cells are LAT, PAG, NTAL and LIME (25). The minireview presents PAG, the only ubiquitously expressed RATRAP, as a potential tumour suppressor, a feature unexpected on its discovery.

First, it should be explained that adaptor proteins are signalling molecules without their own kinase or transcriptional activity but endowed with sequences capable of interactions with other signalling molecules attracting them to the site of action at the right time (25). The next two paragraphs provide necessary background information.

A TOUCH OF CELL SIGNALLING

The general principles of cell signalling delineated below are exploited by a number of cell types. These include membrane receptor activation followed by phosphorylation of first-line kinases with subsequent initiation of phosphorylation cascades with diversification and amplification of the signal before the ultimate targets are reached. The final effect is a sum of 'molecular cross-talk' and can differ in different cell types and under different physiological or pathological conditions (1).

The PAG story started unwinding as a research into early events in immune signalling therefore I shall use immune signalling as an example of the proximal position of PAG and its widespread effects on down-stream kinase cascades.

Immune signalling is triggered by immune receptor engagement followed by phosphorylation of repetitive sequences of immunoreceptor signalling subunits known as immunoreceptor-based activation motifs (ITAMs) executed by Src family kinases (SFK). Phosphorylated ITAMs serve as docking sites for the kinases which take up the second position in signalling cascades, namely kinases of SYK (spleen tyrosine kinase) family; SYK in B-cells and ZAP70 (ζ chain-associated protein 70) in T-cells. These are activated and in turn phosphorylate the next in line effectors and adaptors thereby setting in action several signalling pathways such as NFκB (nuclear factor κB) and MAPK (mitogen